b) cleaving said first and second linkers, thereby releasing said first and second subpopulations from said chip, thereby generating a pool of oligonucleotides comprising said first and second oligonucleotides; and

c) contacting said first and second oligonucleotides with a composition comprising at least a first and second target nucleic acid, whereby said first and second target nucleic acids hybridize with said first and second oligonucleotides whereby said target nucleic acids are detected.

30. (New) A method for multiplex detection of target nucleic acids comprising:

a) cleaving at least first and second different oligonucleotides linked to a substrate through at least a first cleavable linker from said substrate, thereby releasing said first and second oligonucleotides from said substrate generating a pool of oligonucleotides comprising said first and second oligonucleotides; and

b) contacting said first and second oligonucleotides with a composition comprising at least a first and second target nucleic acid, whereby said first and second target nucleic acids hybridize with said first and second oligonucleotides whereby said target nucleic acids are detected.

31. (New) The method according to claim 30, wherein said first and second oligonucleotides are attached covalently through said cleavable linker to said substrate

32. (New) The method according to claim 30, wherein said first and second oligonucleotides are synthesized on said substrate.

REMARKS

Prior to this response and amendment claims 1-16 were pending. As amended herein, claims 1 and 11-16 are canceled. Claims 2-9 are amended and claims 27-32 are new. Support for claims 27-29 is found in claims 1, 11 and 15, respectively, as filed, at p. 21, lines 9-12, and p. 23, lines 10-19. Support for claim 30 is found in the claims as filed and at p. 21, lines 9-12, and p. 23, lines 10-19. Support for new claims 31-32 is found in claims 5 and 6, respectively, as filed.

For the Examiner's convenience a copy of the currently pending claims is attached hereto as Appendix A. A copy of the version showing changes made is attached hereto as Appendix B. Favorable consideration of the following comments relative to the outstanding rejections as they may apply to the present claims is respectfully requested for the following reasons.

RESPONSE TO REJECTIONS

Response to Rejection Under 35 U.S.C. § 102 as anticipated by Holmes

Currently pending Claims 1-16 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Holmes *et al.* (U.S. Patent No 5,679,773) ("Holmes"). The Examiner maintains that Holmes discloses compounds synthesized on solid supports, which may be released upon completion of synthesis, and thus teaches each and every element of the present claims. Applicants respectfully traverse. In addition, Applicants note that the rejection is moot in light of the claim amendments.

Holmes teaches methods for solid phase synthesis of organic molecules. Holmes discloses reagents having attached linking groups, including cleavable linkers, which are useful in solid phase syntheses of high density arrays of organic molecules.

In contrast, the present invention provides methods that include providing a substrate and at least first and second different oligonucleotides linked to the substrate through cleavable linkers, cleaving the linkers, thereby releasing the first and second oligonucleotides from the substrate generating a pool of oligonucleotides that includes the first and second oligonucleotides. The method further includes contacting the pool of oligonucleotides with a composition that includes at least first and second target nucleic acids. The first and second target nucleic acids and first and second oligonucleotides hybridize allowing detection of the target nucleic acids.

As the Examiner is aware, anticipation under 35 U.S.C. § 102 requires that "[f]or a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990).

Here, Applicants submit that nowhere in Holmes is there any teaching of cleaving first and second oligonucleotides from a support as claimed and further contacting the resulting pool of oligonucleotides with a composition that includes at least first and second target nucleic acids for the multiplex detection of target nucleic acids. Although the Examiner notes that Holmes

teaches that following cleavage of oligomers the oligomers could be used in bioassays, Applicants submit that a bioassay is distinct from contacting the pool of oligonucleotides with a composition that includes a first and second target nucleic acid to detect the first and second target nucleic acid. That is, as one of skill in the art would appreciate, a bioassay is an assay that includes analysis of a molecule in a living system. Support for this is found in the Dictionary of Biotechnology , Elsevier Publishing, 1986, which defines a bioassay as "[a] procedure for determining the level or concentration of a substance by measuring its effect on a living system under controlled conditions...." A copy of this definition is included herein as Exhibit A. Thus, Applicants submit that Holmes does not teach methods for multiplex detection of target nucleic acids as presently claimed.

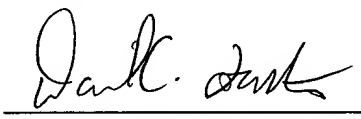
Accordingly, Applicants submit that every element of the claimed invention is not shown in the cited reference, and thus the claims are not anticipated by Holmes. Applicants respectfully request the Examiner to withdraw the rejection.

CONCLUSION

Applicants submit that the claims as amended are in form for immediate allowance and the Examiner is respectfully requested to early notification to that effect. The Examiner is invited to contact the undersigned at (415) 781-1989 if any issues may be resolved in that manner.

Respectfully submitted,

DORSEY & WHITNEY LLP



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Appendix A

COPY OF THE PENDING CLAIMS

Claims 1 and 11-16 are canceled.

2. (Amended) A method according to claim 27, 28, 29 or 30, wherein said first and second oligonucleotides comprise oligonucleotides of known sequence.

3. (Amended) A method according to claim 27, 28, 29 or 30, wherein said first and second oligonucleotides are labeled.

4. (Previously amended) A method according to claim 3, wherein said first and second oligonucleotides bear different labels.

5. (Amended) A method according to claim 27, 28 or 29, wherein said first and second oligonucleotides are attached covalently through said first and second linkers, respectively, to said substrate.

6. (Amended) A method according to claim 27, 28 or 29, wherein said first and second oligonucleotides are synthesized on said substrate.

7. (Amended) A method according to claim 27 and 30, wherein said substrate comprises discrete sites to which said first and second oligonucleotides may be linked.

8. A method according to claim 7, wherein said first and second oligonucleotides are immobilized to first and second beads through first and second linkers, respectively, and wherein said first and second beads are distributed at said discrete sites.

9. (Amended) A method according to claim 27, 29 or 30, further comprising synthesizing said first and second oligonucleotides on said substrate.

10. The method according to claim 9, wherein said first and second oligonucleotides are synthesized by a synthesis method selected from the group consisting of printing and photolithography.

27. (New) A method for multiplex detection of target nucleic acids comprising:

a) providing a substrate and at least first and second different oligonucleotides linked to said substrate through first and second cleavable linkers, respectively;

b) cleaving said first and second linkers, thereby releasing said first and second oligonucleotides from said substrate thereby generating a pool of oligonucleotides comprising said first and second oligonucleotides; and

c) contacting said first and second oligonucleotides with a composition comprising at least a first and second target nucleic acid, whereby said first and second target nucleic acids hybridize with said first and second oligonucleotides whereby said target nucleic acids are detected.

28. (New) A method for multiplex detection of target nucleic acids comprising:

a) providing an array comprising a substrate and a population of oligonucleotides, said population comprising at least first and second subpopulations comprising at least first and second different oligonucleotides, respectively, said first and second oligonucleotides being immobilized to first and second beads, respectively, through first and second cleavable linkers, respectively, said first and second beads being distributed on said substrate;

b) cleaving said first and second linkers, thereby releasing said first and second subpopulations from said first and second beads, thereby generating a pool of oligonucleotides comprising said first and second oligonucleotides; and

c) contacting said first and second oligonucleotides with a composition comprising at least a first and second target nucleic acid, whereby said first and second target nucleic acids hybridize with said first and second oligonucleotides whereby said target nucleic acids are detected.

29. (New) A method for multiplex detection of target nucleic acids comprising:

a) providing an array comprising a substrate and a population of oligonucleotides, said population comprising at least first and second subpopulations comprising at least first and second different oligonucleotides of known sequence, said first and second oligonucleotides being immobilized directly to a chip through first and second cleavable linkers, respectively;

b) cleaving said first and second linkers, thereby releasing said first and second subpopulations from said chip, thereby generating a pool of oligonucleotides comprising said first and second oligonucleotides; and

c) contacting said first and second oligonucleotides with a composition comprising at least a first and second target nucleic acid, whereby said first and second target nucleic acids hybridize with said first and second oligonucleotides whereby said target nucleic acids are detected.

30. (New) A method for multiplex detection of target nucleic acids comprising:

a) cleaving at least first and second different oligonucleotides linked to a substrate through at least a first cleavable linker from said substrate, thereby releasing said first and second oligonucleotides from said substrate generating a pool of oligonucleotides comprising said first and second oligonucleotides; and

b) contacting said first and second oligonucleotides with a composition comprising at least a first and second target nucleic acid, whereby said first and second target nucleic acids hybridize with said first and second oligonucleotides whereby said target nucleic acids are detected.

31. (New) The method according to claim 30, wherein said first and second oligonucleotides are attached covalently through said cleavable linker to said substrate

32. (New) The method according to claim 30, wherein said first and second oligonucleotides are synthesized on said substrate.

Appendix B

Marked up Version of the Claims

1. (Cancel)

2. (Amended) A method according to claim [1] 27, 28, 29 or 30, wherein said first and second oligonucleotides comprise oligonucleotides of known sequence.

3. (Amended) A method according to claim [1] 27, 28, 29 or 30, wherein said first and second oligonucleotides are labeled.

4. (Previously amended) A method according to claim 3, wherein said first and second oligonucleotides bear different labels.

5. (Amended) A method according to claim [3] 27, 28 or 29, wherein said first and second oligonucleotides are attached covalently through said first and second linkers, respectively, to said substrate.

6. (Amended) A method according to claim [3] 27, 28 or 29, wherein said first and second oligonucleotides are synthesized on said substrate.

7. (Amended) A method according to claim [1] 27 and 30, wherein said substrate comprises discrete sites to which said first and second oligonucleotides may be linked.

8. A method according to claim 7, wherein said first and second oligonucleotides are immobilized to first and second beads through first and second linkers, respectively, and wherein said first and second beads are distributed at said discrete sites.

9. (Amended) A method according to claim [1] 27, 29 or 30, further comprising synthesizing said first and second oligonucleotides on said substrate.

10. The method according to claim 9, wherein said first and second oligonucleotides are synthesized by a synthesis method selected from the group consisting of printing and photolithography.

11. (Cancel)

12. (Cancel)

13. (Cancel)

14. (Cancel)

15. (Cancel)

16. (Cancel)

New:

- -27. (New) A method for multiplex detection of target nucleic acids comprising:

a) providing a substrate and at least first and second different oligonucleotides linked to said substrate through first and second cleavable linkers, respectively;

b) cleaving said first and second linkers, thereby releasing said first and second oligonucleotides from said substrate thereby generating a pool of oligonucleotides comprising said first and second oligonucleotides; and

c) contacting said first and second oligonucleotides with a composition comprising at least a first and second target nucleic acid, whereby said first and second target nucleic acids hybridize with said first and second oligonucleotides whereby said target nucleic acids are detected.

28. (New) A method for multiplex detection of target nucleic acids comprising:

a) providing an array comprising a substrate and a population of oligonucleotides, said population comprising at least first and second subpopulations comprising at least first and second different oligonucleotides, respectively, said first and second oligonucleotides being immobilized to first and second beads, respectively, through first and second cleavable linkers, respectively, said first and second beads being distributed on said substrate;

b) cleaving said first and second linkers, thereby releasing said first and second subpopulations from said first and second beads, thereby generating a pool of oligonucleotides comprising said first and second oligonucleotides; and

c) contacting said first and second oligonucleotides with a composition comprising at least a first and second target nucleic acid, whereby said first and second target nucleic acids hybridize with said first and second oligonucleotides whereby said target nucleic acids are detected.

29. (New) A method for multiplex detection of target nucleic acids comprising:

a) providing an array comprising a substrate and a population of oligonucleotides, said population comprising at least first and second subpopulations comprising at least first and second different oligonucleotides of known sequence, said first and second oligonucleotides being immobilized directly to a chip through first and second cleavable linkers, respectively;

b) cleaving said first and second linkers, thereby releasing said first and second subpopulations from said chip, thereby generating a pool of oligonucleotides comprising said first and second oligonucleotides; and

c) contacting said first and second oligonucleotides with a composition comprising at least a first and second target nucleic acid, whereby said first and second target nucleic acids hybridize with said first and second oligonucleotides whereby said target nucleic acids are detected.

30. (New) A method for multiplex detection of target nucleic acids comprising:

a) cleaving at least first and second different oligonucleotides linked to a substrate through at least a first cleavable linker from said substrate, thereby releasing said first and second oligonucleotides from said substrate generating a pool of oligonucleotides comprising said first and second oligonucleotides; and

b) contacting said first and second oligonucleotides with a composition comprising at least a first and second target nucleic acid, whereby said first and second target nucleic acids hybridize with said first and second oligonucleotides whereby said target nucleic acids are detected.

31. (New) The method according to claim 30, wherein said first and second oligonucleotides are attached covalently through said cleavable linker to said substrate

32. (New) The method according to claim 30, wherein said first and second oligonucleotides are synthesized on said substrate. - -.

Exhibit A

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meters such as the are
surface, a heat transfer
exchanger, area across
occurs, area of a sup
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surface in photosynthesis

ABA *See* abscisic acid.

abattoir An animal slaug

abaxial Descriptive of the
or other lateral organ tha
the apex of the axis on v
Compare adaxial.

abomasum The fourth ch
nant stomach.

abortive transduction
bacterial genes into a ne
vector that is not followed
the new genetic material
of the recipient cell. Ho
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cells as plasmid.

abscisic acid (ABA) A pla
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nce Ameasure
ight is attenuated
coloured liquid

A substance

A device

polypeptide chains are linked by hydrogen bonds between imino and carbonyl groups.

Bicine *See* zwitterionic buffer.

biennial A plant which has a life cycle that extends over two growing seasons (two years). In the first season, leaves are often in the form of a prostrate rosette and much of the assimilate is stored in an underground root which overwinters. In the second year, the stored material is used to produce an erect, flowering stem, which then produces seeds.

bilateral symmetry The property of an object in which only one plane, usually passing longitudinally through the midline, divides it into two halves which are mirror images of each other.

bile A secretion of the vertebrate liver that contains cholesterol, bile pigments (biliverdin and bilirubin), bile salts (sodium salts of cholic acid combined with taurine or glycine) and lecithin. It is discharged into the small intestine through the bile duct.

binding site A specific arrangement of atoms or molecules that is recognized by, and forms the point of attachment for, an ion, compound, antibody, virus, cell or organism on another structure or organism.

binomial nomenclature A system for the naming of plants and animals devised by Linnaeus in the 18th century. Each species is given a generic name and a species name. The name of the discoverer is written in an abbreviated form after the species name. The exact procedure and rules for naming new organisms are laid down by the International Codes of Nomenclature. These include the International Code of Nomenclature for Cultivated Plants, the International Code of Botanical Nomenclature and the International Code of Zoological Nomenclature. When a new organism is discovered it is named in Latin, a description is published in the same language and a holotype or type specimen is preserved. In general, the first or oldest name for a given organism takes precedence. Although a given animal or plant must have a name that is unique for the kingdom, in several instances the same name has been given to a plant and an animal. Other oddities occur where stages of the life cycle of a given organism have been placed in different genera or even phyla.

bioassay A procedure for determining the level or concentration of a substance by measuring its effect on a living system under controlled conditions. Compounds such as vitamins, hormones and plant growth substances, which occur in very low concentrations, are often determined using bioassays since such methods are several orders of magnitude more sensitive than conventional chemical analyses.

Bio-beads S A polystyrene support material used in gel filtration chromatography with lipophilic solvents. Produced as a copolymer of styrene and divinylbenzene, it can be used for fractionation of compounds with molecular weights of up to 1.4×10^6.

biocatalysis A catalytic process in which the catalyst consists of, or is derived from, living organisms. The term is applied in particular to processes in which the objective is the production of bulk chemicals or other products of commercial interest.

biocatalyst A catalyst that consists of, or is derived from, a living organism or tissue, or cell culture. Biocatalysts may be categorized as follows:

1) Cells

a) Growing. The use of growing cells in suspension as biocatalysts is generally termed fermentation. Such processes may be distinguished as batch, fed batch or continuous.

b) Non-growing. Non-growing systems include the use of suspensions, cells retained within a semipermeable membrane, or cells immobilized in or on a solid support. Such immobilized cells may be